PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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ETATS-UNIS D'AMERIQUE

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	29.10.2004
Applicant's or agent's file reference X-14844	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 03/16207	11.06.2003	19.06.2002

Applicant
ELI LILLY AND COMPANY et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Roche, S Tel. +49 89 2399-8031

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference X-14844	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US 03/16207	International filing date *(day/month/year)* 11.06.2003	Priority date *(day/month/year)* 19.06.2002
International Patent Classification (IPC) or both national classification and IPC C07C235/20		
Applicant ELI LILLY AND COMPANY et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 22 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
13.01.2004	29.10.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Seufert, G Telephone No. +49 89 2399-8330

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US 03/16207

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-75, 80-89, 91-130, 132-143	as originally filed
76-79, 90, 131	filed with telefax on 16.07.2004

Claims, Numbers

1-41	filed with telefax on 16.07.2004

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

see separate sheet

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-22, 39-41 (part), 29-32 for industrial applicability

because:

☒ the said international application, or the said claims Nos. 29-32 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1-22, 39-41 (part)

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the Standard.

☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-41
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-41
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-28, 33-41
	No:	Claims	

2. Citations and explanations

see separate sheet

Reference is made to the following documents:

D6 DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, Database accession no. 135:257231
D7 WO-A-0063196
D8 WILLSON T M ET AL., vol. 43, no. 4, 24 February 2000, pages 527-550

I. Basis of the opinion

The procedure before the ISA is closed. Thus, with regard to the applicant's request in his reply to the written opinion of 16.07.04 the replacement page 131 of the description has been accepted as amended page according to Art. 34 PCT. The replacement page 153 has been disregarded in view of the amended claims 1-41 submitted on 16.07.04, which already contain the amendments of the aforementioned replacement page.

III. Non establishment of opinion

Claims 29-32 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Furthermore, according to Rule 66.1e the International Preliminary Examination Authority is not required to carry out an examination on subject-matter for which no search report as been established.
The applicant has been informed by the Search Authority that as a consequence of lack of support and disclosure (Art. 5 and 6 PCT) the search report has been established for a group of compounds, which is considered to be supported and has been defined on the supplementary sheet included in the search report. Consequently, the examination of the present invention with regard to novelty, inventive step and industrial applicability has only been carried out for that group of compounds.

V. Reasoned statement under Art. 35(2) PCT with regard to novelty, inventive

step and industrial applicability

Novelty

The present application refers to compounds of the general formula I (claim 1), a pharmaceutical compositions comprising them (claim 28) and their use as a medicine (claim 33). Furthermore, the application refers to specific compounds as described in claims 37-41. The presently claimed compounds are Peroxisome Proliferator Activated Receptor (PPAR) modulators and are therefore useful for the treatment of diabetes, Syndrome X, etc. (claims 29-32, 34, 35).

None of the available documents discloses compounds falling within the scope of claim 1 or 37-41. Claim 1-41 therefore appear to meet the requirement of Art. 33(2) PCT.

Inventive step

Compounds with a Peroxisome Proliferator Activated Receptor (PPAR) modulating activity and their use in the treatment of diabetes, syndrome X, obesity etc. are known in the art, see documents D6-D8. They are distinguished from the presently claimed compounds by their structure, mainly with regard to the substitution on the phenyl ring.

The problem to be solved by the present application was to provide further compounds useful as Peroxisome Proliferator Activated Receptor (PPAR) modulators.

None of the available prior art documents gives an indication to the man skilled in the art to modify the existing prior art compounds in order to arrive at the presently claimed compounds. It was also not obvious that the modified compounds would retain their desired activity. Therefore, the subject-matter of the claims appears to meet the requirements of Art. 33(3) PCT.

Industrial applicability

There are no objections against the industrial applicability of claims 1-28, 33-41.

For the assessment of the present claims 29-32 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The

patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Further remarks:

The definition of R^1 and R^2 under point (f) of claim 1 is considered to be superfluous with regard to the amendments in the definiton under point (a). Furthermore, the definition under (f) is inconsistent with the definition under point (a), which leaves the reader in doubt as to the scope of claim 1 (Art. 6 PCT).

The scope of dependent claim 10 is broader than the scope of claim 1 on which claim 10 depends.

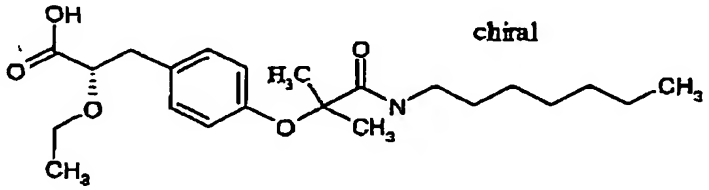
Claim 36 only contains a reference to the description as a technical feature. This claim therefore does not meet the requirements of Art. 6 in combination with Rule 6.2(a) PCT.

In claim 21 the references back to claim 12 appears to be incorrect. In claim 12 the residues R1 and R2 are so defined that they do not form a ring.

Claims 37 and 38 are identical to claims 25 and 26.

EXAMPLE 71

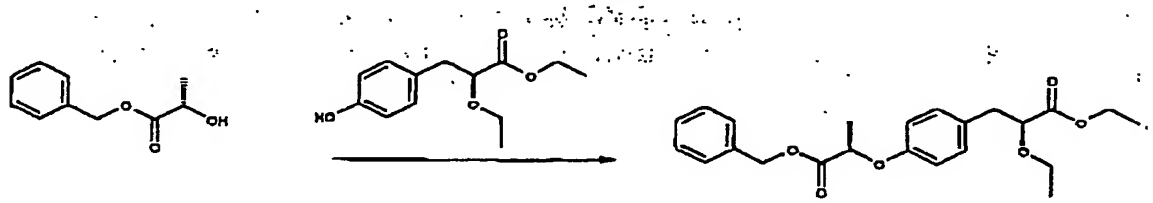
(2S)-2-ethoxy-3-[4-(1-heptylcarbamoyl-1-methyl-ethoxy)-phenyl]-propionic acid



The title compound was prepared from (2S)-3-[4-(1-carboxy-1-methyl-ethoxy)-phenyl]-2-ethoxy-propionic acid ethyl ester (EXAMPLE 49, step 2) and hepthylamine via the same procedure used for the preparation of (2S, 1R)-2-ethoxy-3-(4-{1-[2-(4-phenoxy-phenyl)-ethylcarbamoyl]-ethoxy}-phenyl)-propionic acid (Example 1, step 3) to produce a colorless oil. MS (ES) for $C_{22}H_{33}NO_5$ $[M+H]^+$: 394.

Preparation 6

(R,S)-3-[4-(1-Benzyoxycarbonyl-ethoxy)-phenyl]-2-ethoxy-priopionic acid ethyl ester

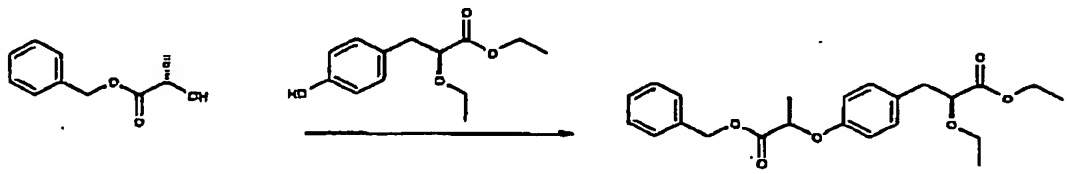


To a solution of 2-(S)-hydroxypropionic acid benzyl ester (0.966 g, 5.36 mmol) and (S)-2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid ethyl ester (1.16 g, 4.88 mmol) in THF (30 ml) was added the triphenyl phosphine (1.66 g, 6.34 mmol). The mixture was cooled to 0 °C and added the DIAD (diisopropyl azodicarboxylate) (1.18 g, 5.86 mmol) dropwise over 5 minutes. The reaction mixture was stirred for 18 hours while warmed to room temperature. The reaction was quenched with water (2 ml) and concentrated to a residue, purified by silica gel chromatography with 20% EtOAc/Hexanes to afford product (1.05 g, 49%) and recovered starting material ((S)-2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid ethyl ester, 0.31 g).

PCT/US2003/016207
X-14844 (PCT) REPLACEMENT PAGE

Preparation 7

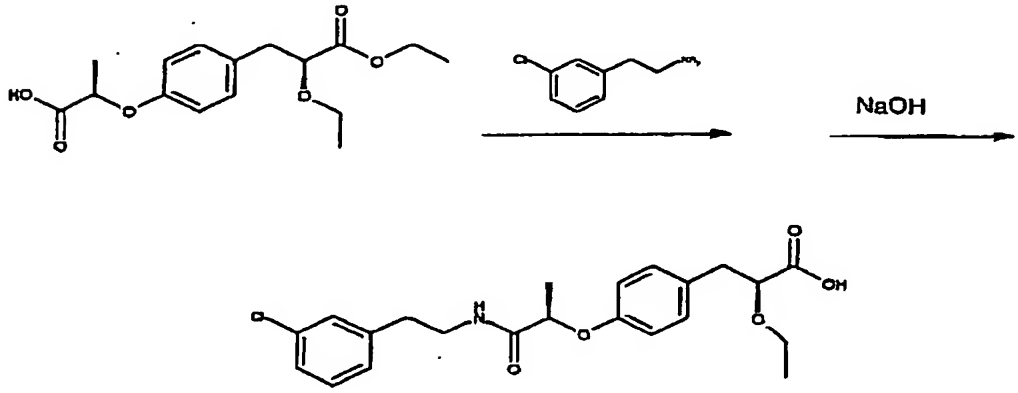
(R,S)-3-[4-(1-Carboxy-ethoxy)-phenyl]-2-ethoxy-propionic acid ethyl ester



To a solution of (R,S)-3-[4-(1-benzyloxycarbonyl-ethoxy)-phenyl]-2-ethoxy-propionic acid ethyl ester (1.05 g, 2.63 mmol) in EtOH (20 ml) and H_2O (0.5 ml) was added a slurry of Pd-C (5%, 100 mg) in EtOH (10 ml). The suspension was hydrogenated under balloon pressure for 2 hours. The mixture was filtered through a pad of celite and concentrated to a residue, the residue was then purified by silica gel chromatography with EtOAc/Hexanes (25% to 100%) to afford the acid product (550 mg, 68%).

Preparation 8

(R,S)-3-(4-{1-[2-(3-Chloro-phenyl)-ethylcarbamoyl]-ethoxy}-phenyl)-2-ethoxy-propionic acid



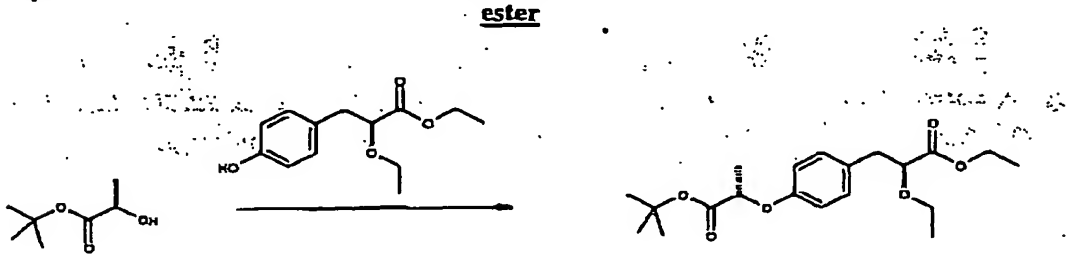
A solution of (R,S)-3-[4-(1-carboxy-ethoxy)-phenyl]-2-ethoxy-propionic acid ethyl ester (310 mg, 1.00 mmol) in CH_2Cl_2 (35 ml) was treated with DMAP (207 mg,

1.70 mmol) and EDC (286 mg, 1.50 mmol). The mixture was stirred at room temperature for 10 minutes and then treated with 3-chlorophenyl ethylamine (201 mg, 1.3 mmol). The reaction mixture was stirred for 2 hours and quenched with NH_4Cl (aq), extracted with CH_2Cl_2 (2x35 ml) and dried over Na_2SO_4 ,purified on silica gel column with EtOAc/Hexanes (20-35%) to yield the intermediate ester product (291 mg, 65%).

The ethyl ester was then dissolved in methanol (2.0 ml) and THF (1.0 ml), and the solution was treated with NaOH (2.0 N, 3.0 ml). The reaction mixture was stirred at room temperature for 18 hours and neutralized with HCl (1.0 N, 6.0 ml) to pH=7 and concentrated. Extracted with EtOAc (3x20 ml), dried over Na_2SO_4 ,purified on silica gel column with EtOAc/Hexanes (35%-100%) and MeOH/EtOAc (5%) to yield the final acid product (130 mg, 29% for two steps).

Preparation 9

(S,S)-3-[4-(1-tert-Butoxycarbonyl-ethoxy)-phenyl]-2-ethoxy-propionic acid ethyl ester

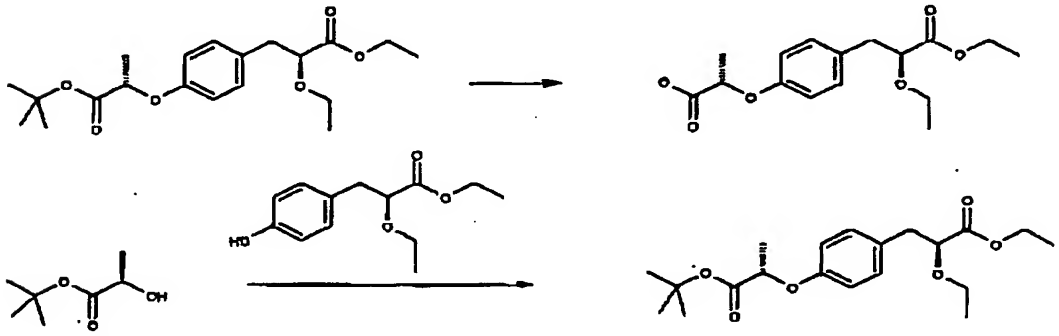


To a solution of 2-(R)-hydroxypropionic acid *tert*-butyl ester (1.23 g, 8.44 mmol) and (S)-2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid ethyl ester (2.01 g, 8.44 mmol) in THF (100 ml) was added the triphenyl phosphine (2.21 g, 8.44 mmol). The mixture was cooled to 0 °C and added the DIAD (diisopropyl azodicarboxylate) (1.70 g, 8.44 mmol) dropwise over 5 minutes. The reaction mixture was stirred for 18 hours while warmed to room temperature. The reaction was quenched with water (2 ml) and concentrated to a residue, purified by silica gel chromatography with 20% EtOAc/Hexanes to afford product (0.99 g, 32%) and recovered starting material ((S)-2-ethoxy-3-(4-hydroxy-phenyl)-propionic acid ethyl ester, 0.85 g).

PCT/US2003/016207
X-14844 (PCT) REPLACEMENT PAGE

Preparation 10

(S,S)-3-[4-(1-Carboxy-ethoxy)-phenyl]-2-ethoxy-propionic acid ethyl ester

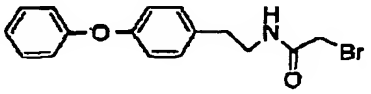


A solution of (S,S)-3-[4-(1-tert-butoxycarbonyl-ethoxy)-phenyl]-2-ethoxy-propionic acid ethyl ester (1.10 g, 3.00 mmol) in CH_2Cl_2 (5.0 ml) and TFA (4.0 ml) and water (0.2 ml) was stirred for 12 hours. The mixture was concentrated to a residue and purified by silica gel chromatography with EtOAc/Hexanes (50%) to afford the acid product (0.91 g, 98%).

H), 2.96 (dd, 1 H, J = 8.3 Hz, 14.2 Hz), 3.04 (dd, 1 H, J = 3.9 Hz, 14.2 Hz), 3.12 (dd, 1 H, J = 6.8 Hz, 14.2 Hz), 3.24 (dd, 1 H, J = 3.4 Hz, 14.2 Hz), 3.39-3.45 (m, 3 H), 3.59-3.65 (m, 1 H), 4.02 (dd, 1 H, J = 4.4 Hz, 7.8 Hz), 4.62 (q, 1 H, J = 3.4 Hz), 6.40 (t, 1 H, J = 5.8 Hz), 6.69 (d, 2 H, J = 8.8 Hz), 6.86 (d, 2 H, J = 7.8 Hz), 7.04 (d, 2 H, J = 8.3 Hz), 7.13(d, 2 H, J = 8.8 Hz), 7.20-7.30 (m, 5 H); MS (M+H): 491.4.

Preparation 11

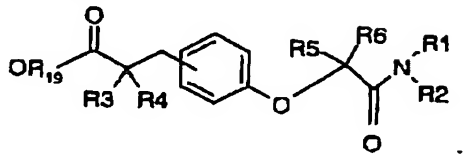
2-Bromo-N-[2-(4-phenoxy-phenyl)-ethyl]-acetamide



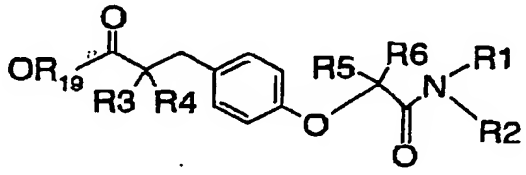
4-phenoxyphenethylamine (213.28 amu, 2.5g, 1eq, 10.8mmol, 1.09 g/mL, 2.3mL) added to a 3-necked flask. Bromoacetyl bromide (201.86 amu, 1.1eq, 11.8mmol, 2.4g, 2.317 g/mL, 1.03mL), pyridine (79.10 amu, 5 eq, 4.27 g, .978 g/mL, 54 mmol, 4.4 mL) added along with 50 mL CH_2Cl_2. Reaction stirred for 2 hours at RT. CH_2Cl_2 removed and mixture taken up in 200mL EtOAc. Organic layer washed with brine and water (200mL each). Organics seperated, dried sodium sulfate, and rotovaped to give 1.56g material. MS [EI+] 334 $(M+H)^+$, MS [EI-] 332 $(M-H)^+$

X-14844 (PCT) REPLACEMENT PAGE

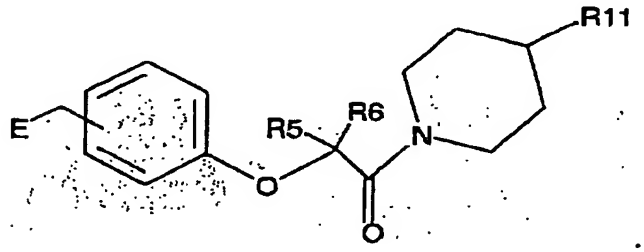
A) A compound of the formula:



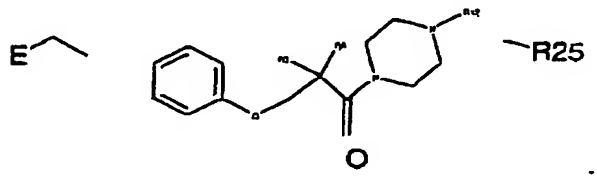
B) A compound of the formula:



C) A compound of the formula:



D) A compound of the formula:



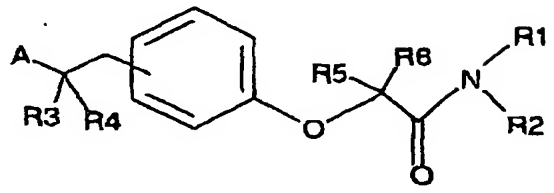
PCT/US2003/016207
X-14844 (PCT) REPLACEMENT PAGE

CLAIMS

What is claimed is:

1. A Compound of the structural formula I:

Formula I



(a) R1 hydrogen or R1 and R2 together form a ring selected from the group consisting of piperidine, piperazine, and dihydroisoquinoline, wherein said piperidine, piperazine, and dihydroisoquinoline is unsubstituted or substituted with from one to three substituents each independently selected from the group consisting of C1-C4 alkyl, phenyl, halophenyl, trifluoromethylphenyl, methylphenyl, methoxyphenyl, acetylphenyl, benzyl, halobenzyl, benzoyl, halobenzoyl, trifluoromethylbenzoyl, methylbenzoyl, methoxybenzoyl, acetyl benzoyl, biphenylmethylene, (phenyl)(halophenyl)methylene, and bihaolophenylmethylene;

(b) R1' and R2' are each independently a group consisting of C_1-C_5 alkyl, C_3-C_6 cycloalkyl, C_1-C_5 alkoxy, arylC_0-C_2alkoxy, haloC_1-C_3alkyl, halo, aryl, -C(O)C_1-C_5alkyl, -C(O)-aryl, haloC_1-C_5alkyloxy, arylC_1-C_5alkyl, and biarylC_1-C_5alkyl; and which -C(O)-aryl is unsubstituted or substituted with from one to three substituents each independently selected from the group consisting of halo, C_1-C_5 alkyl, haloC_1-C_5 alkyl, C_1-C_5 alkoxy, and –C(O)C_1-C_5alkyl; and which C_1-C_5 alkyl, arylC_1-C_5alkyl, biarylC_1-C_5alkyl, and aryl are each independently unsubstituted or substituted with from one to three substituents each independently selected from the group consisting of halo, C_1-C_8alkyl, aryl, haloC_1-C_5 alkyl, trihaloC_1-C_3alkyl, C_1-C_5alkoxy, and arylC_1-C_5alkyl; and which aryl is unsubstituted or substituted with from one to three substituents each independently selected from the group consisting of halo, C_1-C_8alkyl, aryl, haloC_1-C_5 alkyl, trihaloC_1-C_3alkyl, C_1-C_5alkoxy, and arylC_1-C_5alkyl;

(c) R2 is selected from the group consisting of C_1-C_8 alkyl, C_3-C_6 cycloalkyl, aryl-C_{0-4}-alkyl, heteroaryl-C_{0-4}-alkyl, heteroC_1-C_8cycloalkylaryl, heteroC_1-

C_6cycloalkylarylC1-C4alkyl, aminonoC_1-C_4alkyl, C_3-C_6 cycloalkylaryl-C_{0-2}-alkyl, arylheteroC_1-C_8alkyl, C_{0-4}-alkyl-C(O)heteroC_1-C_8alkyl, -CH(C(O)OCH_3)benzyl, and -CH_2-C(O)-R15''-R16'', and which C_1-C_8 alkyl, C_3-C_6 cycloalkyl, aryl-C_{0-4}-alkyl, hetoC_1-C_6cycloalkylaryl, hetoC_1-C_6cycloalkylarylC1-C4alkyl, heteroaryl-C_{0-4}-alkyl, aminoC_1-C_4alkyl, C_3-C_6 cycloalkylaryl-C_{0-2}-alkyl, arylheteroC_1-C_8alkyl, C_{0-4}-alkyl-C(O)heteroC_1-C_8alkyl, and -CH_2-C(O)-R15''-R16'' are each independently unsubstituted or substituted with from one to three substituents each independently selected from the group consisting of R2';

(d) R15'' is O or NH;

(e) R16'' is C_1-C_2 alkyl or benzyl which C_1-C_2 alkyl and benzyl are each unsubstituted or substituted with from one to three substituents each independently selected from the group consisting of R16';

(f) R1 and R2 together may form a heterocyclic ring which heterocyclic ring is unsubstituted or substituted with from one to three substituents each independently selected from the group consisting of R1' and which heterocyclic ring is optionally fused with an aryl;

(g) R7' and R7'' are each independently selected from the group consisting of C_1-C_4 alkyl and C_1-C_4 haloalkyl;

(h) n and m are each independently selected from the group consisting of 0, 1, 2 and 3;

(i) A is selected from the group consisting of $(CH_2)_m$ COOR14, C_1-C_3alkylnitrile, carboxamide, sulfonamide, acylsulfonamide and tetrazole, and which sulfonamide, acylsulfonamide and tetrazole are each independently unsubstituted or substituted with from one to three substituents each independently selected from the group consisting of A';

(j) A' is a group consisting of C_1-C_4alkyl, C_1-C_4 haloalkyl, heteroaryl, and aryl, and wherein heteroaryl and aryl are each independently unsubstituted or substituted with from one to three substituents each independently selected from the group consisting of halo, C_1-C_5 alkyl, C_1-C_5 haloalkyl, C_1-C_5 alkoxy, and –C(O) C_1-C_5 alkyl;

(k) R3 is selected from the group consisting of H, C_1-C_5 alkyl, C_1-C_5 alkenyl, and C_1-C_6 alkoxy;

(l) R4 is selected from the group consisting of H, halo, C_1-C_5 alkyl, C_1-C_6 alkoxy, C_3-C_6 cycloalkyl, aryl C_0-C_4 alkyl, and C_{0-4}alkoxyaryl, and which C_1-C_5 alkyl, C_1-C_5 alkoxy, C_3-C_6 cycloalkyl, aryl C_0-C_4 alkyl, and C_{0-4}alkoxyaryl are each independently unsubstituted or each independently substituted with from one to four substituents each independently selected from R4'; or R3 and R4 are combined to form a C_3-C_6 cycloalkyl;

(m)R5 and R6 are each independently selected from the group consisting of hydrogen, C_1-C_8 alkyl, aryl-C_{0-4}-alkyl, heteroaryl-C_{0-4}-alkyl, C_3-C_6 cycloalkylaryl-C_{0-2}-alkyl, C_3-C_6 cycloalkyl-C_{0-2}-alkyl, and -CH_2-C(O)-R17-R18, and which C_1-C_8 alkyl, aryl-C_{0-4}-alkyl, heteroaryl-C_{0-4}-alkyl, C_3-C_6 cycloalkylaryl-C_{0-2}-alkyl, C_3-C_6 cycloalkyl-C_{0-2}-alkyl, and -CH_2-C(O)-R17-R18 are each independently unsubstituted or substituted with from one to four substituents each independently selected from the group consisting of R5';

(n) R4', R5', and R13'' are each independently a group consisting of C1-C5 alkyl, C1-C5 alkoxy, C1-C5 haloalkyl, C1-C5 haloalkoxy, nitro, cyano, CHO, hydroxy, C_1-C_4 alkanoic acid, phenyl, aryloxy, SO_2R7', SR7'', arylC_0-C_2alkoxy, C1-C6alkylcarboxamido, and COOH;

(o) R16' is a group consisting of halo, C_1-C_8alkyl, aryl, haloalkyl, trihaloC_1-C_3alkyl, C_1-C_5alkoxy, and arylC_1-C_5alkyl;

(p) R17 and R18 are each independently selected from C_1-C_8 alkyl, aryl-C_{0-4}-alkyl, heteroaryl-C_{0-4}-alkyl, C_3-C_6 cycloalkylaryl-C_{0-2}-alkyl, and C_3-C_6 cycloalkyl-C_{0-2}-alkyl;

(q) R14 is selected from the group consisting of hydrogen, C1-C4alkyl, aryl, and arylmethyl, and which C1-C4alkyl are each independently unsubstituted or independently substituted with from one to three substituents each independently selected from the group consisting of R13' and which arylmethyl and aryl are each independently unsubstituted or independently substituted with from one to three substituents each independently selected from the group consisting of R14';

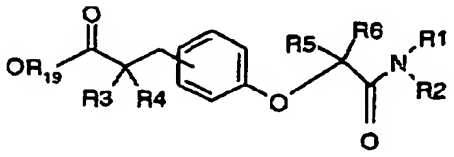
(r) R13' is a group consisting of C_1-C_5 alkyl, C_3-C_6 cycloalkyl, C_1-C_5 haloalkyl, C_1-C_5 alkoxy, aryloxy, halo, aryl, -C(O)C_1-C_5alkyl, -C(O)-aryl, haloC_1-C_5alkyloxy, aryl

C_1-C_5 alkyl, and C_1-C_5 alkylbiaryl, and which –C(O)aryl, aryl, aryl C_1-C_5 alkyl, and C_1-C_5 alkylbiaryl are each independently unsubstituted or substutited with from one to three substituents each independently selected from the group consisting of R13''; and

(s) R14' is a group consisting of halo, C1-C8alkyl, C_1-C_5 haloalkyl, C_1-C_5 alkoxy, and arylC_0-C_4alkyl; or

(t) a pharmaceutically acceptable salt thereof.

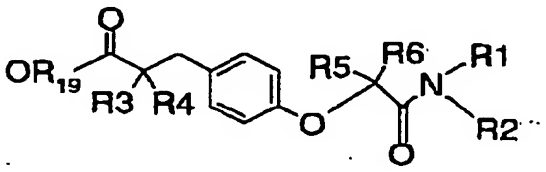
2. A compound as claimed by Claim 1 of the structural Formula II:



II

wherein R19 is selected from the group consisting of hydrogen, C1-C4alkyl, aryl, and arylmethyl, wherein the alkyl, aryl and arylmethyl are each unsubstituted or substituted with from one to three substituents each independently selected from R14'.

3. A compound as claimed by any one of Claims 1 to 2 that is of the following structural formula III:



III

wherein R19 is selected from the group consisting of hydrogen, C1-C4alkyl, aryl, and arylmethyl, wherein the alkyl, aryl and arylmethyl are each unsubstituted or substituted with from one to three substituents each independently selected from R14'.

4. A compound as claimed by any one of Claims 1 to 3 wherein R1 is hydrogen.

5. A compound as claimed by any one of Claims 1 to 4 wherein R2 is selected from the group consisting of arylC_0-C_4alkyl, C_1-C_8 alkyl, heteroarylC_0-C_4alkyl, C_3-C_6 cycloalkyl, C_0-C_4alkyl-C(O)-heteroC_1-C_8 alkyl, arylheteroC_1-C_8alkyl, wherein each of said R2 is unsubstituted or substituted by one or two substituents each independently

selected from the group consisting of phenyl, halophenyl, phenoxy, halo, haloC_1-C_4 alkyl, C_1-C_4alkoxy, and C_3-C_6 cycloalkyl.

6. A compound as claimed by Claim 5 wherein R2 is arylC_0-C_4alkyl wherein the aryl is phenyl or napthyl, and the C_0-C_4alkyl is selected from the group consisting of methyl, ethyl and not present, that is C_0 alkyl.

7. A compound as claimed by Claim 5 wherein R2 is heteroarylC_0-C_4alkyl, and said heteroarylC_0-C_4alkyl is unsubstituted or substituted with from one to three substituents each independently selected from R2'; and wherein the heteroaryl is selected from the group consisting of pyridine, thiazole, benzothiazole, and thiadiazole; and the alkyl is selected from the group consisting of methyl, ethyl and not present, that is C_0 alkyl.

8. A compound as claimed by Claim 5 wherein R2 is arylheteroC_1-C_8alkyl, wherein the arylheteroC_1-C_8alkyl is unsubstituted or substituted with from one to three substituents each independently selected from the group consisting of R2'; wherein the aryl group is phenyl, and the heteroatom is selected from the group consisting of nitrogen, sulfur and oxygen.

9. A compound as claimed by any one of Claims 1 to 8 wherein the R2 group is substituted with one or two substituents each independently selected from the group consisting of methyl, ethyl, t-butyl, fluorine, chlorine, bromine, trifluoromethyl, methoxyl, ethoxyl, phenyl, and phenoxyl.

10. A compound as claimed by Claim 1 wherein said piperidine and piperazine is fused with a phenyl to form a bicyclic ring.

11. A compound as claimed by any one of Claims 1 to 5 or Claims 7 to 9 wherein R2 is unsubstituted or substituted heteroarylC0-C4alkyl; wherein said heteroaryl is selected from the group consisting of:

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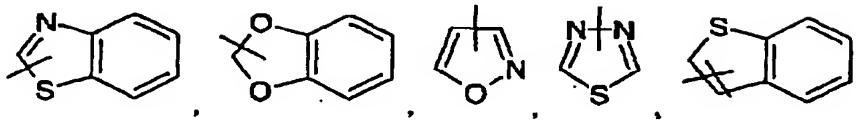
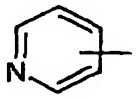

, and.



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12. A compound as claimed by any one of Claims 1 to 3 or 9 wherein R2 is -CH(C(O)OCH$_3$)benzyl.

13. A compound as claimed by any one of Claims 1 to 12 wherein R6 is selected from the group consisting of hydrogen, C_1-C_4 alkyl, and aryl-C_{0-4}-alkyl, wherein the alkyl and arylalkyl are each independently substituted with from one to three substituents each independently selected from the group consisting of R5'.

14. A compound as claimed by any one of Claims 1 to 13 wherein R5 is H or methyl.

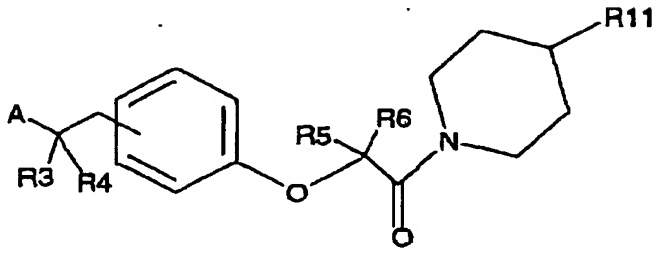
15. A compound as claimed by any one of Claims 1 to 12 or 14 wherein R6 is C_1-C_3 alkyl.

16. A compound as claimed by any one of Claims 1 to 12 or 14 to 15, wherein R6 is methyl.

17. A compound as claimed by any one of Claims 1 or 4 to 16 wherein R5 is hydrogen or methyl, R6 is C_1-C_3 alkyl, and R3 is C_1-C_3alkoxy.

18. A compound as claimed by any one of Claims 1 or 4 to 16 wherein A is C(O)OR26; R26 is H or C_1-C_3alkyl.

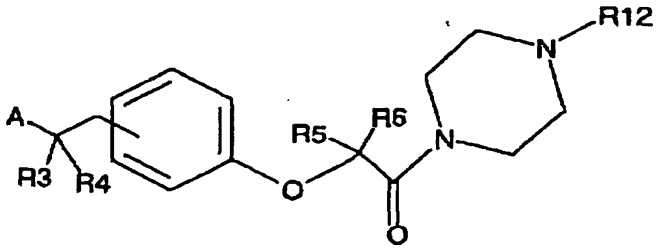
19. A compound as claimed by any one of Claims 1, or 13 to 18 that is of the structural formula IV:



IV

wherein R11 is selected from the group consisting of aryl, -C(O)aryl, haloC_1-C_5alkyloxy, C_1-C_5 alkylaryl, C_1-C_5 alkylbiaryl, aryloxy, and C1-C6 alkyl, wherein the aryl, -C(O)aryl, haloC_1-C_5alkyloxy, C_1-C_5 alkylaryl, C_1-C_5 alkylbiaryl, and C1-C6 alkyl are each independently unsubstituted or each independently substituted with from one to three substituents each independently selected from the group consisting of R1'.

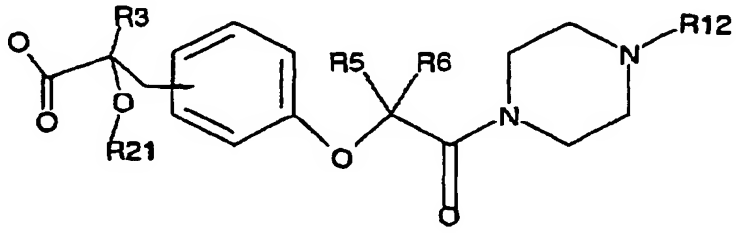
20. A compound as claimed by any one of Claims 1 to 3, or 13 to 18 that is of the structural formula V:



V

wherein R12 is selected from the group consisting of aryl, aryloxy, -C(O)aryl, haloC_1-C_5alkyloxy, C_1-C_5 alkylaryl, C_1-C_5 alkylbiaryl, and C1-C6 alkyl, wherein the aryl, -C(O)aryl, haloC_1-C_5alkyloxy, C_1-C_5 alkylaryl, C_1-C_5 alkylbiaryl, and C1-C6 alkyl are each independently unsubstituted or each independently substituted with from one to three substituents each independently selected from the group consisting of R1'.

21. A compound as claimed by any one of Claims 1, or 12 to 16 that is of the structural formula VII:



VII

wherein wherein R12 is selected from the group consisting of aryl,aryloxy, -C(O)aryl, haloC_1-C_5alkyloxy, arylC_1-C_5 alkyl, C_1-C_5 alkylbiaryl, and C1-C6 alkyl, wherein the aryl, -C(O)aryl, aryloxy, haloC_1-C_5alkyloxy, C_1-C_5 alkylaryl, C_1-C_5 alkylbiaryl, and C1-C6 alkyl are each independently unsubstituted or each independently substituted with from one to three substituents each independently selected from the group consisting of R1'; R25 is selected from the group consisting of C1-C4alkyl, halo, haloC1-C3alkyl, C1-C5 alkoxy, and phenyl.

22. A compound as claimed by any one of Claims 1 to 21 wherein the compound is a pharmaceutically acceptable salt.

23. A compound as claimed by Claim 1 which is selected from the group consisting of:

(2S,1'R)-2-Ethoxy-3-(4-{1'-[2-(4-phenoxy-phenyl)-ethylcarbamoyl]-ethoxy}-phenyl)-propionic acid; (2S,1'R)-2-Ethoxy-3-(4-{1'-[2-(4-ethyl-phenyl)-ethylcarbamoyl]-ethoxy}-phenyl)-propionic acid;(2S,1'R)-2-ethoxy-3-(4-{1'-[2-(4-trifluoromethyl-phenyl)-ethylcarbamoyl]-ethoxy}-phenyl)-propionic acid;

(2S,1'R)-2-ethoxy-3-(4-{1'-[2-(2-ethoxy-phenyl)-ethylcarbamoyl]-ethoxy}-phenyl)-propionic acid;

(2S,1'R)-2-ethoxy-3-{4-[1'-(3-trifluoromethyl-benzylcarbamoyl)-ethoxy]-phenyl}-propionic acid;

(2S,1'R)-2-ethoxy-3-{4-[1'-(3-fluoro-5-trifluoromethyl-benzylcarbamoyl)-ethoxy]-phenyl}-propionic acid;

(2S,1'R)-3-(4-{1'-[(biphenyl-3-ylmethyl)-carbamoyl]-ethoxy}-phenyl)-2-ethoxy-propionic acid;

(2S,1'R)-3-(4-{1'-[2-(3-chloro-phenyl)-ethylcarbamoyl]-ethoxy}-phenyl)-2-ethoxy-propionic acid;

(2S,1'R)-2-ethoxy-3-(4-{1'-[2-(3-fluoro-phenyl)-ethylcarbamoyl]-ethoxy}-phenyl)-propionic acid;

(2S,1'R)-2-ethoxy-3-(4-{1'-[2-(2-fluoro-phenyl)-ethylcarbamoyl]-ethoxy}-phenyl)-propionic acid;

(2S,1'R)-3-(4-{1'-[2-(2,4-dichloro-phenyl)-ethylcarbamoyl]-ethoxy}-phenyl)-2-ethoxy-propionic acid;

(2S,1'R)-3-(4-{1'-[2-(2,6-dichloro-phenyl)-ethylcarbamoyl]-ethoxy}-phenyl)-2-ethoxy-propionic acid;

(2S,1'R)-3-(4-{1'-[2-(2-chloro-phenyl)-ethylcarbamoyl]-ethoxy}-phenyl)-2-ethoxy-propionic acid;(2S,1'R)-3-(4-{1'-[2-(4-tert-butyl-phenyl)-ethylcarbamoyl]-ethoxy}-phenyl)-2-ethoxy-propionic acid;

(2S,1'R)-2-ethoxy-3-{4-[1'-(4-fluoro-benzylcarbamoyl)-ethoxy]-phenyl}-propionic acid;(2S,1'R)-2-ethoxy-3-{4-[1'-(4-trifluoromethyl-benzylcarbamoyl)-ethoxy]-phenyl}-propionic acid;

(2S,1'R)-3-{4-[1'-(4-tert-butyl-benzylcarbamoyl)-ethoxy]-phenyl}-2-ethoxy-propionic acid;(2S,1'R)-3-{4-[1'-(4-tert-butyl-phenylcarbamoyl)-ethoxy]-phenyl}-2-ethoxy-propionic acid;(2S,1'R)-3-{4-[1'-(4-trans-tert-butyl-cyclohexylcarbamoyl)-ethoxy]-phenyl}-2-ethoxy-propionic acid;

(2S)-3-{4-[1-(4-tert-butyl-cyclohexylcarbamoyl)-1-methyl-ethoxy]-phenyl}-2-methoxy-propionic acid;

(2S)-2-methoxy-3-(4-{1-methyl-1-[2-(4-phenoxy-phenyl)-ethylcarbamoyl]-ethoxy}-phenyl)-propionic acid;

(2S)-3-(4-{1-[2-(2-ethoxy-phenyl)-ethylcarbamoyl]-1-methyl-ethoxy}-phenyl)-2-methoxy-propionic acid;

2-methoxy-3-(4-{1-methyl-1-[2-(3-trifluoromethyl-phenyl)-ethylcarbamoyl]-ethoxy}-phenyl)-propionic acid;

(2S)-2-methoxy-3-{4-[1-methyl-1-(3-trifluoromethyl-benzylcarbamoyl)-ethoxy]-phenyl}-propionic acid; (2S)-3-(4-{1-[2-(2-chloro-phenyl)-ethylcarbamoyl]-1-methyl-ethoxy}-phenyl)-2-methoxy-propionic acid;

(2S)-3-(4-{1-[(biphenyl-3-ylmethyl)-carbamoyl]-1-methyl-ethoxy}-phenyl)-2-methoxy-propionic acid;

(2S)-3-(4-{1-[2-(2,5-dimethoxy-phenyl)-ethylcarbamoyl]-1-methyl-ethoxy}-phenyl)-2-methoxy-propionic acid;

(2S)-3-(4-{1-[2-(2-fluoro-phenyl)-ethylcarbamoyl]-1-methyl-ethoxy}-phenyl)-2-methoxy-propionic acid;

(2S)-2-ethoxy-3-(4-{1-methyl-1-[2-(3-trifluoromethyl-phenyl)-ethylcarbamoyl]-ethoxy}-phenyl)-propionic acid;

(2S)-2-ethoxy-3-{4-[1-(3-fluoro-5-trifluoromethyl-benzylcarbamoyl)-1-methyl-ethoxy]-phenyl}-propionic acid;

(2S)-3-(4-{1-[2-(2-chloro-phenyl)-ethylcarbamoyl]-1-methyl-ethoxy}-phenyl)-2-ethoxy-propionic acid;

(2S)-3-(4-{1-[(biphenyl-3-ylmethyl)-carbamoyl]-1-methyl-ethoxy}-phenyl)-2-ethoxy-propionic acid;

(2S)-3-(4-{1-[2-(3-chloro-phenyl)-ethylcarbamoyl]-1-methyl-ethoxy}-phenyl)-2-ethoxy-propionic acid;

(2S)-3-(4-{1-[2-(2,5-dimethoxy-phenyl)-ethylcarbamoyl]-1-methyl-ethoxy}-phenyl)-2-ethoxy-propionic acid;

(2S)-2-ethoxy-3-(4-{1-[2-(2-fluoro-phenyl)-ethylcarbamoyl]-1-methyl-ethoxy}-phenyl)-propionic acid;

(2S)-3-{3-[1-(4-tert-butyl-cyclohexylcarbamoyl)-1-methyl-ethoxy]-phenyl}-2-methoxy-propionic acid;

(2S)-3-{3-[1-(3-fluoro-5-trifluoromethyl-benzylcarbamoyl)-1-methyl-ethoxy]-phenyl}-2-methoxy-propionic acid;

(2S)-3-(3-{1-[(biphenyl-3-ylmethyl)-carbamoyl]-1-methyl-ethoxy}-phenyl)-2-methoxy-propionic acid;

(2S)-3-(3-{1-[2-(3-chloro-phenyl)-ethylcarbamoyl]-1-methyl-ethoxy}-phenyl)-2-methoxy-propionic acid;

(2S)-2-methoxy-3-{4-[(1-phenyl-ethylcarbamoyl)-methoxy]-phenyl}-propionic acid;

(2S)-3-(3-{1-[2-(2,4-dichloro-phenyl)-ethylcarbamoyl]-1-methyl-ethoxy}-phenyl)-2-methoxy-propionic acid;

(2S)-3-(3-{1-[2-(2,6-dichloro-phenyl)-ethylcarbamoyl]-1-methyl-ethoxy}-phenyl)-2-methoxy-propionic acid;

(2S)-3-(4-{1-[2-(2,4-dichloro-phenyl)-ethylcarbamoyl]-1-methyl-ethoxy}-phenyl)-2-methoxy-propionic acid;

(2S)-3-(4-{1-[2-(2,4-dichloro-phenyl)-ethylcarbamoyl]-1-methyl-ethoxy}-phenyl)-2- ethoxy-propionic acid;

(2S)-3-(4-{1-[2-(2,6-dichloro-phenyl)-ethylcarbamoyl]-1-methyl-ethoxy}-phenyl)-2-ethoxy-propionic acid;

(2S)-2-ethoxy-3-(4-{1-[2-(4-ethyl-phenyl)-ethylcarbamoyl]-1-methyl-ethoxy}-phenyl)-propionic acid;

(2S)-2-ethoxy-3-(4-{1-[2-(2-ethoxy-phenyl)-ethylcarbamoyl]-1-methyl-ethoxy}-phenyl)-propionic acid;

2-Ethoxy-3-{4-[1-(3-trifluoromethyl-benzylcarbamoyl)-ethoxy]-phenyl}-propionic acid;

2-Ethoxy-3-{4-[1-(5-fluoro-3-trifluoromethyl-benzylcarbamoyl)-ethoxy]-phenyl}-propionic acid;

2-Ethoxy-3-{4-[1-(3-phenyl-benzylcarbamoyl)-ethoxy]-phenyl}-propionic acid;

2-Ethoxy-3-{4-[1-(4-phenoxy-phenylethylcarbamoyl)-ethoxy]-phenyl}-propionic acid;

2-Ethoxy-3-{4-[1-(3-trifluoromethyl-phenylethylcarbamoyl)-ethoxy]-phenyl}-propionic acid;

3-(4-{1-[2-(2,6-Dichloro-phenyl)-ethylcarbamoyl]-ethoxy}-phenyl)-2-ethoxy-propionic acid;

2-Ethoxy-3-(4-{1-[2-(4-ethyl-phenyl)-ethylcarbamoyl]-ethoxy}-phenyl)-propionic acid;

2-Ethoxy-3-(4-{1-[2-(4-ethyl-phenyl)-ethylcarbamoyl]-ethoxy}-phenyl)-propionic acid;

3-(4-{Cyclohexyl-[2-(4-ethyl-phenyl)-ethylcarbamoyl]-methoxy}-phenyl)-2-ethoxy-propionic acid;

2-Ethoxy-3-(4-{1-[2-(4-ethyl-phenyl)-ethylcarbamoyl]-2-phenyl-ethoxy}-phenyl)-propionic acid; and

(2S,1'R)-2-ethoxy-3-{4-[1'-(2-thiophen-2-yl-ethylcarbamoyl)-ethoxy]-phenyl}-propionic acid; or pharmaceutically acceptable salts thereof.

24. A compound as claimed by Claim 1 wherein the compound is selected from the group consisting of

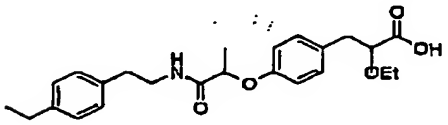
(2S,1'R)-3-{4-[1'-(4-tert-butyl-cyclohexylcarbamoyl)-ethoxy]-phenyl}-2-ethoxy-propionic acid;

(2S,1'R)-2-ethoxy-3-(4-{1'-[(thiophen-2-ylmethyl)-carbamoyl]-ethoxy}-phenyl)-propionic acid;

(2S,1'R)-2-ethoxy-3-{4-[1'-(2-thiophen-2-yl-ethylcarbamoyl)-ethoxy]-phenyl}-propionic acid; or

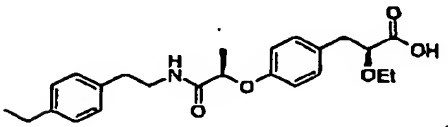
pharmaceutically acceptable salts thereof.

25. A compound as claimed by Claim 1 wherein the compound is



; or a pharmaceutically acceptable salt thereof.

26. A compound as claimed by Claim 1 wherein the compound is



; or a pharmaceutically acceptable salt thereof.

27. A compound as claimed by any one of Claims 1 through 26 which is the hemipiperazine salt.

28. A pharmaceutical composition, comprising a pharmaceutically acceptable carrier and at least one compound as claimed by any one of Claims 1-27 or a pharmaceutically-acceptable-salt-thereof.

29. A method of modulating a peroxisome proliferator activated receptor, comprising the step of contacting the receptor with at least one compound as claimed by any one of Claims 1-27 or a pharmaceutically acceptable salt thereof.

30. A method of treating diabetes mellitus in a mammal, comprising the step of administering to the mammal a therapeutically effective amount of at least one compound of Claims 1-27 or a pharmaceutically acceptable salt thereof.

31. A method of preventing diabetes mellitus in a mammal, comprising the step of administering to the mammal an effective amount of at least one compound of Claims 1-27 or a pharmaceutically acceptable salt thereof.

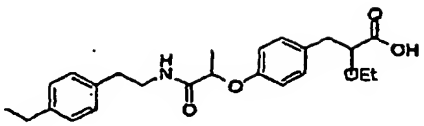
32. A method of treating Syndrome X in a mammal, comprising the step of administering to the mammal a therapeutically effective amount of at least one compound of Claims 1-27 or a pharmaceutically acceptable salt thereof.

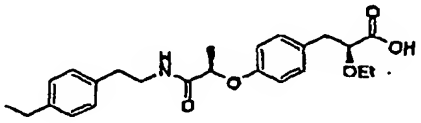
33. A compound or pharmaceutically acceptable salt thereof according to any one of Claims 1 through 27 for use as a medicine.

34. Use of a compound or pharmaceutically acceptable salt thereof as defined in any one of Claims 1 to 27 for the manufacture of a medicament for the treatment or prevention of diabetes mellitus in a mammal.

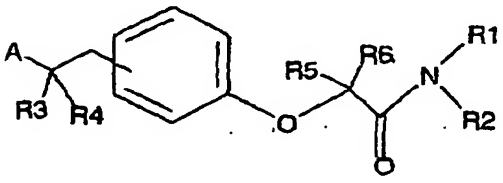
35. Use of a compound or pharmaceutically acceptable salt thereof as defined in any one of Claims 1 to 27 for the manufacture of a medicament for the treatment of Syndrome X in a mammal.

36. A compound as disclosed by any one of the examples herein.

37. A compound of the formula:  ; or a pharmaceutically acceptable salt thereof.

38. A compound of the formula:  ; or a pharmaceutically acceptable salt thereof.

39. A compound of the formula



wherein R1 is selected from the group consisting of hydrogen, C_1-C_4 alkyl, and arylC_0-C_4alkyl; R2 is selected from the group consisting of arylC_0-C_4alkyl, and heteroarylC_0-C_4alkyl; or a pharmaceutically acceptable salt thereof.

41. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and at least one compound as claimed by Claim 40.